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U.S.-JAPAN COMPETITION IN PHARMACEUTICALS: NO CONTEST?

SUMMARY

Pharmaceuticals are a perennial favorite of American business journalists looking for the next U.S. industrial stronghold to be tested by Japanese competitors. Perennial is the operative word. Japan's biggest pharmaceutical companies made significant strides during the 1980s, adding second- or third-generation compounds in several therapeutic classes to product portfolios previously made up largely of licensed drugs. Nonetheless, it will take another five to 10 years before any Japanese player can hope to compete in the same league as the top American and European manufacturers. In an industry where competitiveness is practically synonymous with the ability to develop and introduce a small but steady stream of innovative, profitable products, Japanese makers simply do not have enough drugs on the market or coming through the development pipeline to move up to the majors sooner.

Even the five- to 10-year time frame may be optimistic. Innovation hinges largely on the ability to finance research and development, and here Japan's pharmaceutical industry could come up short. Leading Japanese drug companies now earmark roughly the same proportion of revenues for R&D as major U.S. suppliers, but the absolute amounts are of a different order of magnitude because competitors in Japan have much smaller sales bases. Moreover, Japanese producers are having trouble sustaining the yearly increases in R&D spending that put them on a par with the U.S. industry's leaders even while the costs of developing new products continue to climb. The government's drug pricing system with its alternate-year cuts in national health insurance reimbursement rates is the major cause of the unimpressive to poor sales and earnings of top Japanese pharmaceutical companies in recent years, but stiffer competition from American and European pharmaceutical heavyweights in the local market also is taking a toll on the domestic industry's financial results.

To break out of the earnings slump first-tier Japanese pharmaceutical manufacturers are trying to expand markets in the United States and Europe for their

latest innovative products by buying or setting up production bases and distribution networks as backstops to licensing arrangements. Globalization, however, is a slow process, and the leaders of the U.S. pharmaceutical industry are not standing still. Top American drug makers, consistently the most profitable group of companies on the Fortune 500 list, continue to expand annual R&D spending by double-digit figures. Mergers have better positioned several big competitors to handle the high and increasing costs of new drug development. Other producers have forged strategic alliances to achieve the same objective. Coming on top of their own problems, moves like these will keep Japanese players in the minor league for the foreseeable future.

Unorthodox Advancement Policy

It's easy to write off U.S. manufacturers as across-the-board losers in the 1990s. After all, Japanese competitors have stripped American companies of world market leadership in industry after industry and put them on the defensive in still others; European rivals have added to this country's competitiveness problems in the same or different industries. But blanket pessimism, although understandable, is not warranted. Industry and trade analysts both in the government and outside have little trouble coming up with important industries where U.S. predominance appears unassailable at least through the end of this decade. Their candidates differ, but one industry is common to virtually all the scorecards — pharmaceuticals.

On paper pharmaceuticals should be on the casualty list as well. Drug companies in Japan got the same industrial policy leg up in the 1960s that gave steel, car, semiconductor and other current world-class Japanese manufacturers a big head start in the international catch-up process — a protected home market. Unable to own more than 50 percent of a drug manufacturing and/or marketing subsidiary in Japan from 1964 until mid-1975, many American and European makers of prescription medicines did what Tokyo expected and licensed their products to local companies for production or import and distribution. Japanese pharmaceutical producers also used the country's patent system in the adaptive way intended by industrial policy planners. Prior to 1976 patents in Japan were granted only on new processes, never on substances. That meant domestic drug firms legally could produce copies of prescription products developed by foreign suppliers simply by coming up with a different, unprotected production method.

Japan's pharmaceutical industry actually had two potentially major built-in competitive advantages: a nurturing industrial policy plus a supportive health care policy. In 1961 Tokyo created a national health insurance system that at the time generously covered prescription drug costs. And, in an unusual move, the government allowed doctors not only to prescribe but also to dispense drugs bought at negotiated prices and pocket the difference between what they charged patients and the amounts reimbursed. That combination guaranteed a fast-expanding market for prescription pharmaceuticals. The Ministry of Health and Welfare's early drug approval process helped Japanese companies capitalize on this growth since before 1967 any pharmaceutical preparation approved for sale by the Food and Drug Administration or the regulatory authority of another country did not have to be retested in Japan.

Although the alliance of industrial and health care policies made pharmaceutical companies the high fliers of Japanese industry in the 1960s and 1970s, this pairing steered manufacturers in the direction of licensing products from American and European companies rather than developing new

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drugs of their own — the prerequisite for an internationally competitive pharmaceutical industry. Innovation incentives unquestionably were in place. The drug reimbursement system, for example, was structured to favor domestically developed products at the expense of established brand names. Moreover, the spur to license foreign products inherent in Japan's drug approval process was minimized by the 1967 requirement that most preclinical work and all clinical testing performed overseas had to be repeated in Japan before a new product approval application could be submitted to MHW. Similarly, the mid-1975 end to the restrictions on inward foreign investment lessened the pressure on American and European manufacturers to license their products. In addition, the 1976 extension of legal protection to the active ingredient in a pharmaceutical compound made the development of "me-too" products less attractive. On balance, though, the system retained its bias for licensed products well into the 1980s.

This tilt notwithstanding, Japan had the nucleus of a research-oriented pharmaceutical industry by the start of the 1980s. Made up of a dozen or so first-tier companies led by Takeda Chemical Industries, Ltd., Sankyo Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd. and a roughly equal number of smaller makers, this group appeared poised to put Japan at the top of the world pharmaceutical industry. The 1982-84 tally of new drug introductions, a convenient proxy for international competitiveness, had Japan first with 29 compounds, the United States next at 25, followed by West Germany with 11 substances — a flip-flop of the country rankings during the 1970s when the United States introduced 159 new drugs, West Germany brought 87 to market and Japan unveiled 73 products.

Using new drug introduction numbers as a guide to current or future competitiveness can produce misleading conclusions since the country totals say nothing about the innovativeness of the products developed. Like the third-generation cephalosporin antibiotics dotting the 1982-84 Japan list, almost all of the drugs credited to Japanese pharmaceutical manufacturers during the 1970s and in the first half of the 1980s were follow-up products, not breakthrough substances or even truly innovative compounds. That highlighted the dilemma faced by research-oriented Japanese drug makers. With R&D budgets far smaller than major American and European manufacturers, Japanese companies were forced to concentrate resources on incremental improvements in drugs already on the market — greater efficacy or improved safety, for example. But generational products, although counted as original chemical entities, do not generate the money needed to fund work on the more innovative compounds that make pharmaceutical manufacturers world competitors.

Industrial Policy Collides With Cost Containment

Any hopes Japan's research-oriented pharmaceutical companies harbored of getting off the treadmill of limited innovation and low profits in the 1980s were destroyed by a reordering of MHW health care policy priorities at the start of the decade. Medical expenditures in Japan had quadrupled during the 1960s and then more than tripled in the 1970s. Convinced that the government's national health insurance bill would continue to climb at double-digit rates without remedial action, MHW policymakers quickly zeroed in on NHI's drug reimbursement program. That program was an obvious target. By 1980 pharmaceutical preparations, including over-the-counter products as well as prescription drugs, represented at least one-third of Japan's medical expenditures. The comparable figure for the United States was a much lower 8 percent or so and edging down as a share of health care spending.

MHW's solution for Japan's seemingly runaway drug costs was to bring the government-set rates at which medical institutions and doctors are reimbursed for the drugs they use or dispense (NHI or official drug prices) into line with the wholesale prices pharmaceutical companies charge hospitals and medical practioners. The competition-caused difference was calculated at roughly 10 to 20 percent for most drugs at the beginning of the 1980s but up to 40 percent for some products. Before the gap could be attacked, however, NHI prices had to be established for every brand-name prescription drug on the market rather than for groups of products with similar therapeutic effects, the previous practice. That process, still in effect today for new drugs, yielded the highest price at which any drug

Japan. Differences among NHI prices for comparable products generally reflected premiums awarded to compounds developed in Japan, bonuses for medically useful drugs and/or credits for limited-demand but medically necessary medicines.

Armed with its list Chuikyo (Central Social Insurance Medical Council), a MHW advisory group, began to cut reimbursement prices on a brand-by-brand basis in mid-1981. By March 1990 NHI drug prices cumulatively had been slashed by a whopping 70.6 percent on average, with the initial reduction of 18.6 percent followed by drops of 4.9 percent in 1983, 16.6 percent in 1984, 6 percent in 1987, 5.1 percent in 1986, 10.2 percent in 1988 and 9.2 percent in 1990. These cuts did what MHW intended. The yearly rise in national medical expenditures was trimmed during the 1980s to the low single-digit range, and the proportion of gross national product spent on health care was kept close to 5 percent throughout the period. But cost containment also stranded Japan's pharmaceutical industry.

Production of prescription and nonprescription pharmaceuticals and related products expanded 60.7 percent between 1980 and 1990 or from ¥3.5 trillion ($15.4 billion*) to ¥5.6 trillion ($38.7 billion) (see Appendix). Not a bad showing at first glance, this gain was far smaller than the growth in output during the 1970s. Moreover, it paled in comparison with the 169.6 percent jump in U.S. shipments of drugs (broadly defined) from the larger starting base of $17.7 billion to $47.7 billion in 1990. The major cause of the slowdown is intuitively obvious: medical institutions and doctors forced drug producers to swallow most of the cuts in NHI reimbursement rates through lower wholesale prices. Part of the problem, however, was the still prominent production position of drugs licensed from overseas, which often were lower-priced compounds than products developed in-house. Another contributing factor was the continued dependence of leading Japanese pharmaceutical makers on antibiotics, infamous for their short product cycles and pricing pressures. At the same time drug companies had trouble coming up with enough new products in such growth areas as cardiovascular agents to counter the declining production value of antibiotics.

The last explanation has a certain irony. Japanese drug industry R&D spending climbed 140.2 percent over the course of the 1980s, going from ¥189.8 billion ($873.8 million) in FY 1980 to ¥456 billion ($3.2 billion) in FY 1989. This expansion raised the proportion of sales revenues invested in R&D by 1.5 percentage points to 7.5 percent for the 348 companies doing research and/or development work in the last reporting year. It also kept Japanese companies ahead in the international new drug introduction sweepstakes. Manufacturers headquartered in Japan put 84 prescription products on the market over the course of the 1985,90 period versus 72 for American companies; West German firms were a distant third (20).

Derivative products remained the norm for developed-in-Japan drugs, however. No wonder. Already the world's big spenders, the 100-plus U.S. makers of prescription pharmaceuticals accelerated their investments in ethical drug R&D in the 1980s, boosting outlays from $2 billion at the start of the decade to $7.3 billion at the end and lifting the R&D/sales ratio from 8.8 percent to 14.6 percent. The payoff from this spending volume was documented in a 1990 French study. Using the internationally recognized gauge of true innovation in the pharmaceutical industry — discoveries of new chemical entities that eventually are sold in the world's seven major markets, the author identified 33 such American-developed products in the 1975-84 period. The comparable number for European manufacturers was 39; for Japanese companies it was five. During the 1985-89 time frame, however, the U.S. industry moved into a class by itself, coming up with 14 global NCEs compared with five for its European counterpart and zero for Japan.

A 1991 International Trade Commission study provided yet another measure of the competitive gap between Japanese pharmaceutical makers and, in this case, American and European manufacturers. Looking at the largest companies in each of these three groups, researchers found that the average Japanese top-nine firm had 28 prescription drugs developed in-house in its product

*Unless otherwise noted all yen figures are converted into dollars at the relevant year's average exchange rate.

portfolio during the 1987-89 period. In contrast, the 11 U.S. producers surveyed marketed an average of 53 ethical compounds from their own corporate laboratories, while the nine European businesses in the sample had 52 apiece. Interestingly, though, licensed prescription drugs represented almost the same share of the average Japanese, American and European maker's product line-up — one-fourth, although the actual numbers varied (10, 16 and 18, respectively).

Japan's leading prescription drug manufacturers did not need the French study or the ITC survey to tell them they still had a long way to go. All they had to do was look at their own financial statements and then glance at the annual reports put out by the top U.S. drug companies. The largest pharmaceutical sales gain posted by a major Japanese maker in FY 1990 was 9.3 percent, and that increase was rung up by Yamanouchi Pharmaceutical Co., Ltd., which has perhaps the strongest development capabilities of the industry's big companies. (According to one estimate, 90 percent of Yamanouchi's sales in FY 1989 were generated by products it developed.) Moreover, reaching sales of ¥213.2 billion ($1.5 billion) in the year through March 1991 took the help of six drugs in the early stages of their product cycles plus strong-seller Gaster, a treatment for peptic ulcers and gastritis.

Sankyo, the industry's number-two producer, also did well by Japanese standards in the April 1990-March 1991 period, raising drug sales 7.7 percent to ¥292.7 billion ($2.1 billion). Its performance demonstrated that a below-average ratio of products developed in-house is not a deterrent to modest growth if a company can come up with at least one big-selling compound. For Sankyo that product was Mevalotin, a cholesterol-reducing agent, which had revenues of ¥45.6 billion ($322.8 million) in its first full year on the market.

At the other end of the scale was industry leader Takeda. Its pharmaceutical sales slipped in FY 1989 and then dropped 11.5 percent in the next accounting period to ¥368.3 billion ($2.1 billion). Takeda had to contend with several problems in FY 1990. That year's 9.2 percent average cut in NHI drug prices hit the company harder than some of its competitors because of the large number of established products in the corporate portfolio, including a fairly high proportion of licensed drugs. Moreover, new-to-the-market Pansporin T, an oral cephalosporin, and Calslot, a calcium channel blocker for hypertension, had respectable but not outstanding sales in Japan. Takeda also lost a contract from Bayer AG in April 1990 to distribute a heart medication in Japan for the big German maker.

Were it an American company Takeda would not make the list of the 10 biggest U.S. drug makers. That roster is headed by Merck & Co., Inc., which again doubled as the world industry leader in 1990 with pharmaceutical sales of $7.1 billion. Contributing to its 17.5 percent revenue jump were 18 prescription drugs in nine therapeutic classes that had worldwide sales of at least $100 million during the year, including top-selling Vasotec (an angiotensin converting enzyme or ACE inhibitor for reducing high blood pressure and treating congestive heart failure), Mevacor (a cholesterol-lowering agent) and five other antihypertensives and cardiovasculars.

Merck's 1990 sales gain was not only typical of what other big American companies achieved that year but in line with the U.S. ethical drug industry's growth during the late 1980s. For example, Bristol-Myers Squibb Co., the number-two domestic pharmaceutical manufacturer and third worldwide after the United Kingdom's Glaxo Holdings PLC, boosted drug sales 15.2 percent in 1990 to $7 billion. This total reflected revenues of $100 million-plus for 11 prescription drugs led by ACE inhibitor Capoten, which had global sales of more than $1 billion during the year.

With their huge and fast-expanding sales Merck, Bristol-Myers Squibb and other big U.S. drug manufacturers have the money to keep multiple new prescription products moving through the development pipeline and to cover the enormous costs of clinical and other testing. Merck alone invested $854 million in R&D in 1990, up from $233.9 million in 1980. Last year it spent nearly $1 billion, a figure roughly equal to 10 percent of R&D spending by U.S. ethical drug producers and 5 percent of worldwide expenditures. In 1992 the company, universally recognized for its productive use of R&D funds, expects to pour $1.1 billion into research and development, about the same amount

earmarked by Glaxo. Bristol-Myers Squibb and Johnson & Johnson have comparably sized R&D budgets. Although part of both companies' budgets goes for work outside the pharmaceutical business, spending on prescription drug R&D represented 14.4 percent of the number-two U.S. maker's ethical pharmaceutical sales in 1990 and 15.3 percent of Johnson & Johnson's.

More money does not guarantee successful innovation in the ethical drug industry, but it certainly gives competitors a better chance of coming up with the next blockbuster product instead of a new version of an existing drug. By this benchmark Japan's research-oriented makers appear doomed. While some fairly sizable funding increases during the late 1980s put most major Japanese companies on an equal footing with top U.S. pharmaceutical makers in terms of R&D/ethical drug sales ratios, Japan's eight largest drug manufacturers together invested only ¥223.5 billion ($1.6 billion) in research and development in FY 1990. Moreover, part of that money went for projects in other business lines.

Makers of prescription products could get some help from the latest changes in the NHI drug pricing system. Frustrated by the continuing 20 percent-plus spread between reimbursement rates and actual wholesale prices — a difference MHW pegged in 1990 at ¥1.3 trillion ($9.1 billion) a year, Chuikyo recommended a revamp of the price adjustment mechanism in May 1991. Until then a so-called 90 percent bulk-line method had been used to determine changes in NHI prices for most drugs already on the market. Under that formula if there were 100 different selling prices for a particular product, the ninetieth highest price was adopted as the official price. To ensure that future NHI prices for established drugs more closely tracked market prices the MHW advisory group opted for the use of a drug's actual weighted-average price as its official price.

Along with this methodology Chuikyo proposed that the NHI price for a specific product not be cut if the drug's actual weighted-average price were no more than 15 percent below the reimbursement rate. Prescription drug manufacturers, both foreign and Japanese, had fought hard for pricing relief of this type, arguing that at a minimum producers should be allowed some margin for inflation. Their idea of a reasonable safety zone was 20 percent, however. To boot, the MHW panel recommended that the 15 percent figure be lowered in three steps to 10 percent in 1998.

Chuikyo's suggested price-setting formula for new prescription drugs earned more applause from the Japan Pharmaceutical Manufacturers Association and its American counterpart. Although comparative data still would be used to establish basic NHI prices for new products, a premium of up to 20 percent would be added for genuinely innovative drugs, whether developed in Japan or overseas. Bonuses worth a maximum of 3 percent apiece also would be applied to "useful" new drugs — for example, drugs exhibiting fewer side effects than products already on the market — and orphan drugs.

The advisory group's price adjustment formula was used to calculate the April 1992 NHI prices for existing drugs. That process yielded a bigger cut than pharmaceutical manufacturers had anticipated, 8.1 percent on average. Analysts do not know for certain why the reduction exceeded the expected 7 percent or so decrease, but they have one candidate: new drug distribution practices that went into effect a year ago. As a result of those changes — part of a broader, U.S.-inspired effort by the Fair Trade Commission to streamline Japan's distribution system and make it more transparent, the power to negotiate drug prices with medical institutions and doctors basically shifted from manufacturers to wholesalers.

Previously drug companies determined the prices at which wholesalers resold products to end users. Now inexperienced wholesalers are making those decisions. They reportedly are being maneuvered by the medical establishment into pricing products below what had been manufacturers' resale quotes, with the deepest discounts occurring in those therapeutic classes like antibiotics where considerable pricing pressures existed even under the old system. The apparent result over the last year was a bigger-than-realized decline in the actual weighted-average price of a broad range of prescription medicines, which pulled down NHI reimbursement rates for FY 1992. That experience

does not bode well for an end to the downward price spiral that has constrained the Japanese industry's drug development efforts. It also calls into question the competitive value of the revised system for setting NHI prices for new pharmaceutical products.

Breaking In ...

Cost containment unquestionably is the Japanese pharmaceutical industry's number-one competitive problem, but aggressive American and European drug makers also are making it hard for research-oriented companies to generate money at home for innovation. Freed from the restraints that hamstrung their early activities, foreign multinationals have built a major presence in the world's second-largest drug market over the last decade. Today they have a direct stake of at least 20 percent in Japan's prescription and over-the-counter drug business, plus an additional but hard-to-quantify share of the market through licensing arrangements. Virtually to a company, though, major American, German, Swiss and British producers regard their current slice of Japanese ethical drug sales (2.3 percent at most, according to one study of the 1989 market) as just a beginning.

Leading international pharmaceutical manufacturers used the 1980s to complete the first stage of their strategic plans for becoming major players in the Japanese market and concurrently to launch the next phases. For companies that went into Japan during the period of restricted investment opportunities or even before then, step one involved converting joint venture manufacturing and/or marketing operations into wholly owned subsidiaries or gaining management control of joint ventures while making provision for future full ownership. Bristol-Myers, Pfizer Inc. (the number-five U.S. pharmaceutical maker), Warner-Lambert Co. (another top-10 American drug manufacturer), Glaxo and Switzerland's Ciby-Geigy AG were among the firms buying out Japanese partners. For their part SmithKline Beckman Corp. and Monsanto Co.'s G.D. Searle & Co. pharmaceutical unit both arranged to take over their joint ventures in the 1990s. Merck's phase-one strategy was the most creative. Instead of buying out its longtime production and sales joint venture partner, Banyu Pharmaceutical Co., Ltd., the world industry leader acquired a 50.02 percent stake in the midsized drug maker in October 1984.

Gaining complete or majority control of their Japanese operations gave foreign manufacturers the freedom to pursue relationships with other drug makers in Japan, but in divorcing partners that were competitors American and European producers often lost their distributors. That marked the start of phase two for most companies: building or expanding in-house sales organizations. Multinationals like Pfizer and Germany's Hoechst AG that went the direct distribution route from the start or offshore suppliers that used a combination of direct sales and distributors, such as Bayer and Switzerland's Sandoz Ltd., had demonstrated that foreign companies could recruit a Japanese marketing team. The main problems encountered by these firms as well as Schering-Plough Corp., Eli Lilly and Co. and other foreign manufacturers that established their own sales networks during the 1980s were the expense and the time required to develop competitive in-house marketing organizations.

Industry analysts say a pharmaceutical maker needs a minimum of 800 sales people to have a market impact in Japan and a marketing force of at least 1,000 to cover hospitals and doctors across Japan as effectively as Takeda, Sankyo, Yamanouchi and other major Japanese manufacturers. Merck reportedly has crossed the second threshold, while Bayer — which shares the foreign market leadership position in Japan with the top U.S. drug company — and Pfizer are at or near the first one. With anywhere from 500 to 700 marketing representatives on board now and additional people being hired, competitors like Glaxo, Ciba-Geigy, Sandoz, Hoechst, Schering-Plough and Upjohn Co. are within striking distance. To achieve the necessary market coverage, however, a few firms in this category as well as foreign companies with smaller in-house sales staffs use Japanese distributors for part or all of their product line.

While expanding their marketing units, major American and European drug manufacturers also are strengthening their R&D presence in Japan. A 1990 MHW survey indicated that 29 of 49

foreign-affiliated pharmaceutical companies in Japan already had local research centers and that six others planned similar facilities. Most of these laboratories conduct or oversee clinical work on new drugs developed overseas preparatory to filing a product approval application with the ministry. (While Japan has accepted foreign clinical test findings in principle since mid-1985, tests must be repeated in Japan if the results can be affected by racial differences — absorption, metabolism and excretion tests, dosage determination tests and comparative clinical trials.) Nevertheless, an increasing number of foreign-owned facilities, like the one Merck will open this spring for research on cancer and cardiovascular and infectious diseases, are geared for basic and applied research or development work.

... and Out

With aggressive foreign multinationals compounding their money-making troubles at home, Japan's leading drug manufacturers took a harder look in the second half of the 1980s at the largely unexplored area of direct sales in the United States and Europe. Until then pharmaceutical makers felt they had no option other than granting American and European drug companies production and sales rights to their most innovative products. The difficulties of navigating the rigorous FDA new drug approval process in this country and comparable regulatory hurdles in Europe plus the cost and time problems associated with organizing adequate marketing networks overseas simply overwhelmed corporate marketing strategists.

Yet, as Japanese pharmaceutical makers first discovered when they assigned offshore manufacturing and marketing rights to their cephalosporin antibiotics in the 1970s, licensing arrangements also have a major drawback: they are more profitable for the licensee than the product's developer. Take, for example, Herbesser, a calcium antagonist developed by Tanabe Seiyaku Co., Ltd. The world's leading treatment for hypertension and angina, it is marketed in this country by Marion Merrell Dow Inc. as Cardizem. U.S. sales totaled $743 million in 1990 alone, but Japan's eighth-largest drug maker saw little of this money or what the drug made in the nearly 100 other countries outside Japan in which it is sold

Japan's technology trade figures quantify the disadvantages of licensing. Despite a steady increase in the number of drugs licensed for foreign sale during the 1980s, royalties and fees earned by Japan's pharmaceutical industry merely expanded from ¥8.3 billion ($36.3 million) in FY 1981 to ¥18.9 billion ($132.4 million) in FY 1989. To make matters worse Japanese drug makers continued to pay out more for products licensed from American and European manufacturers than they earned after going into the black in FY 1986 and FY 1987. With payments running at ¥21.5 billion ($150.4 million) in the April 1989-March 1990 period, the difference was not much smaller than in FY 1981 when outlays totaled ¥11.1 billion ($48.6 million). Even the addition of exports to licensees of bulk ingredients, such as diltiazem (Herbesser's generic name), or ready-to-dispense drugs did not alter the fact that Japanese drug companies needed an overseas presence if they were to make real money in the international market.

Takeda made the earliest move in this direction, forming an equally owned venture with Abbott Laboratories in 1977 to develop and sell prescription products in North America based on the top Japanese drug maker's research. The mainstay of TAP Pharmaceutical Inc. is Lupron, marketed on introduction in 1985 as a treatment for advanced prostate cancer and since 1990 as a treatment for endometriosis. Takeda's subsequent U.S. move was to open a plant in Wilmington, North Carolina in 1986 for the production of vitamin B_1 and later vitamin C, both of which are marketed in the United States and Canada by a wholly owned American subsidiary.

Although it was the first major Japanese pharmaceutical manufacturer to venture abroad, Takeda has moved more cautiously than some of its rivals in both the United States and Europe, where the company's activities are limited to marketing arrangements for Lupron (known there as Enantone) with German, French and Italian firms. Yamanouchi, for instance, built a plant in Dublin, Ireland for bulk shipments of its Gaster (famotidine) ulcer medicine to licensee Merck for European sale starting in mid-1989 and American marketing at the beginning of 1990. In 1991 the Irish facility

added bulk production of Perdipine (nicardipine), a calcium antagonist. The same year the number-three Japanese pharmaceutical maker bought the drug division of a small Dutch company to give it a foothold in the European market similar to the stake it had acquired in the United States through the 1989 purchase of Shaklee Corp. While Shaklee makes nutritional supplements rather than prescription drugs, the buyout gave Yamanouchi access to American management skills, a research center, a manufacturing facility and a distribution network, all of which can be adapted for the production and sale of ethical drugs.

Acquisitions also have given Fujisawa European and American business bases. The number-four Japanese drug company owns a 74 percent interest in Klinge Pharma GmbH, a German developer and maker of cardiovascular and respiratory system agents that has a sales force of about 1,000 people. Klinge's European manufacturing operations will be supplemented by a Fujisawa plant nearing completion in Ireland; that facility will be used to formulate and package FK-506, a promising immunosuppressant, for the American and European markets. The center of the Japanese manufacturer's U.S. operations is the former LyphoMed Inc. The suburban Chicago, Illinois-headquartered producer of injectable drugs used in hospitals was bought in a two-step process completed in 1989. This purchase not only supplied Fujisawa with three domestic plants and an independent American research capability but also boosted its existing U.S. sales and marketing force to about 300 people.

For its part Sankyo acquired a midsized German pharmaceutical company, Luitpold-Werk AG. That 1990 move also provided entree to the American market through Luitpold's New York production and sales subsidiary. But this and the similar overseas steps taken by Sankyo's at-home rivals merely position leading Japanese research-oriented pharmaceutical companies for possible future international growth. The infrastructure now in place in the United States and Europe, while a start, simply is not extensive enough to give a significant near- or medium-term boost to the financial position of top Japanese drug makers. In addition, potentially big-selling current prescription products already have been licensed to foreign companies for international sale, including Sankyo's Mevalotin, which will be marketed outside Asia by Bristol-Myers Squibb. That also apparently is true for most of the Japanese-developed ethical drugs now in the testing phase.

Moreover, while Japan's major prescription drug manufacturers are building foreign production and/or sales bases, American and European multinationals are becoming stronger competitors. A merger wave took place during the 1980s, driven in large part by the high and rising cost of new drug development. (According to the most widely quoted estimate, developing a new chemical entity in the United States and bringing it to market costs $231 million if the R&D charges associated with failed drugs are included.) The 1989 merger of Squibb Corp. with Bristol-Myers Co., both top-10 U.S. drug manufacturers on their own, headed combinations that included in the same year the acquisition of SmithKline Beckman by the United Kingdom's Beecham Group plc, another major international player; the purchase of medium-sized A.H. Robins Co. by American Home Products Corp., the number-two American maker until Squibb and Bristol-Myers merged; and the takeover of midsized Marion Laboratories Inc. by Dow Chemical Co.'s Merrell Dow unit. Merck matched these strategic moves with one of its own, forming an equally owned joint venture with E.I. duPont de Nemours & Co., Inc. in 1990 to discover, develop and market prescription drug products in several therapeutic classes. Other major American and European drug makers also have merged, formed research alliances, licensed-in products or signed comarketing deals for certain products. Moves like these will make it hard if not possible for Japan's top ethical pharmaceutical companies to enter the international major league of drug manufacturers.

For further information, contact **Susan MacKnight.**

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The views expressed in this report are those of the author and do not necessarily represent those of the Japan Economic Institute.

APPENDIX

Table 1: **Japan's Pharmaceutical Market, 1980-90**

	1980	1985	1986	1987	1988	1989	1990
			(in millions of yen)				
Production	¥3,482,177	¥4,001,807	¥4,280,732	¥4,825,398	¥5,059,459	¥5,502,271	¥5,595,435
Total Exports* (f.o.b.)	n.a.	30,487	30,447	30,412	28,216	27,351	35,746
Total Imports* (c.i.f.)	262,363	308,954	329,741	355,496	376,006	417,861	469,486
Trade Balance	n.a.	-278,467	-299,294	-325,084	-347,790	-390,510	-433,740
Exports to United States* (f.o.b.)	n.a.	2,815	3,019	1,655	1,101	1,221	1,899
Imports from United States* (c.i.f.)	71,243	120,007	112,885	104,063	101,007	109,418	124,425
Trade Balance	n.a.	-117,192	-109,866	-102,408	-99,906	-108,197	-122,526
Total Exports as Percent of Production	n.a.	0.8%	0.7%	0.6%	0.6%	0.5%	0.6%
Total Imports as Percent of Apparent Domestic Consumption	n.a.	7.2%	7.2%	6.9%	7.0%	7.1%	7.8%
Exports to United States as Percent of Production	n.a.	0.1%	0.1%	--	--	--	--
Imports from United States as Percent of Apparent Domestic Consumption	n.a.	2.8%	2.5%	2.0%	1.9%	1.9%	2.1%
			(in millions of dollars**)				
Production	$15,358	$16,776	$25,402	$33,361	$39,481	$39,883	$38,645
Total Exports* (f.o.b.)	n.a.	127	179	208	220	199	246
Total Imports* (c.i.f.)	1,152	1,286	1,939	2,435	2,934	3,044	3,236
Trade Balance	n.a.	-1,159	-1,760	-2,227	-2,714	-2,845	-2,990

*Covers only pharmaceutical products in final, ready-to-use, form. The much bigger two-way trade in bulk ingredients is excluded.

**The following average exchange rates were used to convert the yen figures into dollars:

Production - 1980, ¥226.74; 1985, ¥238.54; 1986, ¥168.52; 1987, ¥144.64; 1988, ¥128.15; 1989, ¥137,96; and 1990, ¥144.79.

Exports - 1980, ¥227.67; 1985, ¥240.29; 1986, ¥169.99; 1987, ¥145.90; 1988, ¥128,13; 1989, ¥137.34; and 1990, ¥145.10.

Imports - 1980, ¥227.85; 1985, ¥240.17; 1986, ¥170.08; 1987, ¥146.01; 1988, ¥128.15; 1989, ¥137.26; and 1990, ¥145.09.

Source: Ministry of Health and Welfare, Pharmaceutical Affairs Bureau, *Yakuji Kogyo Seisan Dotai Tokei Nenpo*.

Table 2: **Production of Pharmaceuticals in Japan, 1980-90***

(in millions of yen)

	1980	1985	1986	1987	1988	1989	1990
Cardiovascular Agents	¥377,757	¥519,683	¥563,301	¥648,509	¥695,987	¥770,008	¥828,331
Antibiotics and Anti-Infectives	814,320	690,505	683,361	733,974	702,485	724,523	624,117
Central Nervous System Agents	344,197	383,855	430,516	494,766	517,456	559,001	548,292
Gastrointestinal Agents	256,830	353,799	372,044	436,969	458,256	522,300	521,601
Miscellaneous Metabolic Agents	363,950	314,132	328,629	368,335	396,390	436,562	465,934
Dermatological Agents	197,984	239,679	261,030	284,322	303,865	324,902	325,928
Vitamins	216,249	238,541	243,712	252,574	267,369	282,518	286,811
Respiratory System Agents	79,960	141,781	166,904	202,518	222,294	248,310	265,383
Diagnostic Agents	30,164	65,019	72,236	110,548	145,160	166,617	202,235
Blood Pressure and Similar Medicines	82,690	121,405	132,270	144,597	151,937	176,569	178,690
Nutrients and Tonics	85,704	126,021	129,274	146,571	151,937	167,686	172,193
Biologicals	114,396	153,359	157,887	114,550	145,160	159,805	171,651
Antitumor Agents	107,351	138,601	160,822	144,597	148,853	166,517	164,151
Chemotherapy Drugs	29,487	59,020	82,269	109,622	107,162	118,963	162,053
Herb Medicines	33,749	75,273	93,233	110,548	117,602	137,770	161,756
Other Pharmaceutical Preparations	347,389	381,134	403,244	522,600	527,546	540,220	516,309
Total	3,482,177	4,001,807	4,280,732	4,825,398	5,059,459	5,502,271	5,595,435
of which:							
Prescription	2,978,437	3,383,710	3,649,842	4,141,820	4,309,824	4,676,456	4,720,333
Domestic Drugs	1,981,278	2,386,022	2,547,249	2,897,396	2,991,784	3,230,933	3,324,858
Imported Drugs	997,159	997,688	1,102,593	1,244,424	1,318,040	1,445,523	1,395,475
Nonprescription	503,740	618,096	630,890	683,577	749,634	825,815	875,103

Note: Imported prescription drugs are compounds made primarily from imported ingredients, including raw powder, undiluted solutions and bulk goods.

*Ranked in terms of 1990 output.

Source: Ministry of Health and Welfare, Pharmaceutical Affairs Bureau, *Yakuji Kogyo Seisan Dotai Tokei Nenpo*.

Table 3: **Japan's Exports of Pharmaceuticals, 1980-90**

(in millions of yen)

	1980	1985	1986	1987	1988	1989	1990
Total Exports	n.a.	¥30,487	¥30,447	¥30,412	¥28,216	¥27,351	¥35,746
By Major Market*							
People's Republic of China	n.a.	3,262	4,616	6,356	7,085	4,931	6,987
Taiwan	n.a.	4,913	5,406	4,888	5,074	5,008	4,909
Hong Kong	n.a.	1,875	2,363	2,386	2,480	2,320	2,762
East Germany	n.a.	n.a.	n.a.	673	1,037	2,002	2,295
South Korea	n.a.	1,360	1,324	1,288	1,616	1,525	2,005
United States	n.a.	2,815	3,019	1,655	1,101	1,221	1,899
West Germany	n.a.	1,867	1,952	1,917	638	768	1,395
By Major Product Line*							
Antibiotics and Anti-Infectives	n.a.	6,161	6,062	7,546	7,341	5,867	6,418
Diagnostic Agents	n.a.	5,816	5,465	5,312	3,334	3,559	5,999
Nutrients and Tonics	n.a.	2,057	3,418	2,933	3,695	3,454	5,059
Antitumor Agents	n.a.	1,101	1,542	1,718	1,456	1,851	2,223
Miscellaneous Metabolic Agents	n.a.	1,257	1,329	1,185	1,033	884	2,011
Exports to the United States by Major Product Line							
Antibiotics and Anti-Infectives	n.a.	409	342	n.a.	n.a.	208	441
Diagnostic Agents	n.a.	1,365	1,539	643	224	351	750
Nutrients and Tonics	n.a.	324	549	539	382	489	432
Miscellaneous Metabolic Agents	n.a.	130	177	140	98	n.a.	107

Note: These export figures cover only pharmaceutical products in final, ready-to-use, form. Excluded are exported bulk ingredients.

*Ranked in terms of 1990 trade.

Source: Ministry of Health and Welfare, Pharmaceutical Affairs Bureau, *Yakuji Kogyo Seisan Dotai Tokei Nenpo.*

Table 4: **Japan's Imports of Pharmaceuticals, 1980-90**

(in millions of yen)

	1980	1985	1986	1987	1988	1989	1990
Total Imports	¥262,363	¥308,954	¥329,741	¥355,496	¥376,006	¥417,861	¥469,486
of which:							
Prescription	n.a.	302,602	321,627	348,235	366,646	407,441	457,505
By Major Supplier*							
United States	71,243	120,007	112,885	104,063	101,007	109,418	124,425
West Germany	52,161	59,506	71,161	80,046	85,167	100,316	108,587
Great Britain	13,727	29,883	36,825	51,171	41,954	50,109	55,617
Switzerland	29,309	18,101	25,405	26,704	36,653	35,627	39,739
By Major Product Line*							
Diagnostic Agents	3,257	45,130	65,331	83,677	91,841	112,882	144,856
Hormones	28,908	32,987	36,827	40,066	41,714	49,295	66,461
Biologicals	15,662	81,574	69,608	63,204	61,705	66,698	64,561
Antibiotics and Anti-Infectives	88,880	37,658	32,022	33,080	42,669	43,843	37,694
Sensory Organ Agents	n.a.	9,381	11,259	13,368	16,902	19,739	23,617
Imports from the United States by Major Product Line							
Diagnostic Agents	n.a.	15,191	19,550	24,837	25,759	31,979	48,900
Hormones	n.a.	8,955	9,624	9,999	9,609	10,723	11,278
Biologicals	n.a.	73,926	61,801	51,944	49,671	51,184	48,625
Antibiotics and Anti-Infectives	n.a.	7,713	8,321	8,909	8,989	10,699	10,343
Sensory Organ Agents	n.a.	91	146	117	1,053	57	287

Note: These import figures cover only pharmaceutical products in final, ready-to-use, form. Excluded are imported bulk ingredients. Their total is indicated on Table 2.

*Ranked in terms of 1990 trade.

Source: Ministry of Health and Welfare, Pharmaceutical Affairs Bureau, *Yakuji Kogyo Seisan Dotai Tokei Nenpo*.

Table 5: **R&D Spending by Japan's Pharmaceutical Industry**

Expenditures on Disbursement Basis

	FY 1980	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989
Total (in millions of yen)	¥189,838	¥341,880	¥341,978	¥380,701	¥416,220	¥455,950
Total (in thousands of dollars*)	$873,823	$1,546,339	$2,139,502	$2,751,724	$3,245,127	$3,192,257
Share of Sales	6.00%	7.04%	6.89%	6.96%	6.94%	7.50%

Note: The data were converted into dollars at the following average exchange rates: FY 1980, ¥217.25; FY 1985, ¥221.09; FY 1986, ¥159.84; FY 1987, ¥138.35; FY 1988, ¥128.26; and FY 1989, ¥142.83.

Spending by Sales Volume, FY 1989

Sales Volume (million yen)	Number of Companies	Total Sales (million yen)	Net Operating Income (million yen)	Total R&D Personnel	Total R&D Spending (million yen)	Share of Sales*
Total	575	¥6,250,800	¥657,439	26,040	¥455,950	7.50%
Under ¥100	78	5,000	71	7	26	6.40
¥100-¥1,000	209	83,700	4,078	271	1,713	4.93
¥1,000-¥10,000	199	615,300	50,410	3,407	32,926	5.75
¥10,000 or More	89	5,546,900	602,880	22,355	421,286	7.70

*For those companies performing R&D.

Type of R&D Spending by Size of Capital, FY 1989

Capital (million yen)	Number of Companies	R&D Spending (million yen)				Distribution		
		Total	Basic	Applied	Development	Basic	Applied	Development
Total	348	¥455,950	¥95,286	¥122,195	¥238,470	20.9%	26.8%	52.3%
¥5-¥10	10	131	9	8	114	6.7	6.0	87.3
¥10-¥100	195	18,243	3,103	3,501	11,640	17.0	19.2	63.8
¥100-¥1,000	77	41,041	8,933	13,345	18,762	21.8	32.5	45.7
¥1,000-¥10,000	45	106,444	12,373	31,326	62,744	11.6	29.4	58.9
¥10,000 or More	21	290,092	70,867	74,015	145,210	24.4	25.5	50.1

Source: Management and Coordination Agency, Statistics Bureau, *Report on the Survey of Research and Development.*

Table 6: **Financial Profiles of Japan's Major Pharmaceutical Makers, FY 1988-FY 1990**

(in millions of yen)

	Worldwide Pharmaceutical Sales	Total Sales	Share of Non-Japan Sales	Total Operating Income	Total R&D Spending	Share of Total Sales
Takeda Chemical Industries, Ltd.						
FY 1988	¥420,041	¥585,015	5%	¥65,244	¥43,868	7.5%
FY 1989	416,257	587,763	6	60,127	48,500	8.3
FY 1990	368,264	550,871	9	54,964	49,400	9.0
Sankyo Co., Ltd.						
FY 1988	266,861	308,510	2	28,462	23,495	7.6
FY 1989	271,788	313,731	4	29,707	24,785	7.9
FY 1990	292,706	336,311	5	40,933	24,785	7.4
Yamanouchi Pharmaceutical Co., Ltd.						
FY 1988	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
FY 1989	195,051	195,051	8	46,002	22,245	11.4
FY 1990	213,183	213,183	9	47,302	26,197	12.3
Fujisawa Pharmaceutical Co., Ltd.						
FY 1988	192,995	208,643	5	11,057	22,318	10.7
FY 1989	192,192	210,303	7	10,444	24,404	11.6
FY 1990	201,744	221,209	8	11,241	27,578	12.5
Eisai Co., Ltd.						
FY 1988	173,362	186,411	4	29,706	24,732	13.3
FY 1989	182,676	197,274	4	29,866	27,400	13.9
FY 1990	192,341	205,493	4	28,969	29,400	14.3
Shionogi & Co., Ltd.						
FY 1988	183,666	216,077	1	25,925	20,420	9.5
FY 1989	179,367	213,223	1	22,518	22,714	10.7
FY 1990	182,233	215,790	1	12,856	24,478	11.3
Daiichi Pharmaceutical Co., Ltd.						
FY 1988	166,734	166,734	5	39,091	17,159	10.3
FY 1989	169,257	169,257	7	37,798	18,480	10.9
FY 1990	178,045	178,045	8	32,011	20,976	11.8
Tanabe Seiyaku Co., Ltd.						
FY 1988	167,165	196,665	17	21,533	16,136	8.2
FY 1989	164,800	193,200	18	11,706	17,600	9.1
FY 1990	170,990	200,223	18	11,203	20,642	10.3

Notes: Pharmaceuticals cover both ethical and over-the-counter drugs.
For some companies the FY 1988 figure for worldwide pharmaceutical sales was partially estimated.
The data can be converted into dollars using the following average exchange rates: FY 1988, ¥128.26; FY 1989, ¥142.83; and FY 1990, ¥141.28.

Source: Toyo Keizai Inc., *Japan Company Handbook*, and company reports.

Table 7: **U.S. Pharmaceutical Market, 1980-90**

(in millions of dollars)

	1980	1985	1986	1987	1988	1989	1990
Total Shipments	$17,674.3	$29,718.8	$32,110.3	$35,283.4	$39,327.7	$42,687.4	$47,650.3
Total Exports (f.a.s.)	n.a.	2,671.0	3,087.0	3,229.0	3,934.0	4,346.0	5,062.0
of which:							
Pharmaceutical Preparations	n.a.	691.0	648.0	676.0	858.0	974.0	1,258.0
Medicinals and Botanicals	n.a.	1,465.0	1,815.0	1,982.0	2,463.0	1,797.0	1,921.0
Biologicals	n.a.	516.0	623.0	571.0	614.0	837.0	973.0
Diagnostic Substances	n.a.	n.a.	n.a.	n.a.	n.a.	739.0	909.0
Total Imports (Customs)	n.a.	1,896.0	2,322.0	2,795.0	3,485.0	3,513.0	3,863.0
of which:							
Pharmaceutical Preparations	n.a.	216.0	157.0	164.0	199.0	868.0	1,103.0
Medicinals and Botanicals	n.a.	1,517.0	2,007.0	2,468.0	3,056.0	2,336.0	2,282.0
Biologicals	n.a.	163.0	158.0	164.0	230.0	191.0	271.0
Diagnostic Substances	n.a.	n.a.	n.a.	n.a.	n.a.	118.0	207.0
Trade Balance	n.a.	775.0	765.0	434.0	449.0	833.0	1,199.0
Exports to Japan (f.a.s.)	n.a.	n.a.	n.a.	n.a.	n.a.	915.0	877.0
Imports from Japan (Customs)	n.a.	n.a.	n.a.	n.a.	n.a.	418.0	360.0
Trade Balance	n.a.	n.a.	n.a.	n.a.	n.a.	497.0	517.0
Total Exports as Percent of Shipments	n.a.	9.0%	9.6%	9.2%	10.0%	10.2%	10.6%
Total Imports as Percent of Apparent Domestic Consumption	n.a.	6.6%	7.4%	8.0%	9.0%	8.4%	8.3%

Note: The trade data for the 1985-88 period and the 1989-90 period are not directly comparable because of the switch in 1989 to the Harmonized Commodity Description and Coding System.

Table 8: **U.S. Shipments of Pharmaceuticals, 1980-90**

(in millions of dollars)

	1980	1985	1986	1987	1988	1989	1990
Central Nervous System and Sensory Organ Agents	$2,821.0	$5,737.6	$5,946.0	$5,740.5	$6,172.7	$6,441.3	$7,290.7
Antibiotics and Anti-Infectives	1,778.3	3,386.2	3,821.0	4,024.9	4,593.6	4,936.2	5,612.1
Cardiovascular Agents	1,176.4	3,170.9	3,570.3	3,795.9	4,449.9	4,874.9	5,321.3
Gastrointestinal and Genitourinary Agents	1,232.3	1,875.9	1,864.5	2,954.8	3,860.8	4,363.0	4,940.4
Respiratory System Agents	1,239.5	2,202.4	2,492.2	2,811.4	3,224.0	3,286.2	3,917.5
Hormones and Antitumor Agents	1,209.7	2,110.2	2,140.6	1,994.9	2,071.2	2,507.4	2,784.4
Vitamins and Nutrients	1,876.5	2,291.2	2,665.9	2,570.7	2,538.5	2,672.4	2,662.7
Dermatological Agents	728.1	1,213.3	1,327.3	1,288.3	1,388.5	1,451.7	1,548.6
Veterinary Preparations	546.3	817.7	853.7	997.1	1,051.5	1,071.1	1,022.8
Unspecified Preparations	306.2	544.6	590.3	431.7	0.0	0.0	0.0
Pharmaceutical Preparations	12,914.3	23,350.0	25,271.9	26,610.3	29,350.7	31,604.2	35,100.6
of which:							
Prescription	7,814.2	15,110.0	16,468.1	17,756.4	20,014.6	22,171.3	25,109.5
Nonprescription	4,530.2	7,177.8	7,673.5	7,807.7	8,814.7	8,726.5	9,291.1
Bulk Shipments	263.8	517.6	540.0	614.5	521.4	706.5	699.9
Medicinals and Botanicals*	3,158.0	3,347.3	3,397.2	4,224.4	4,948.1	5,392.6	5,788.9
Biologicals**	1,602.0	1,328.3	1,419.0	1,765.3	1,966.0	2,219.9	2,526.8
Diagnostic Substances	n.a.	1,693.2	2,022.2	2,683.4	3,062.9	3,470.7	4,234.0
Total Shipments	17,674.3	29,718.8	32,110.3	35,283.4	39,327.7	42,687.4	47,650.3

*Medicinals are made up largely of bulk organic and inorganic medicinal chemicals and their derivatives, while botanicals consist mainly of bulk botanical drugs and herbs.

**Biologicals include vaccines, antigens, antitoxins and toxoids as well as serums, plasmas and other blood derivatives. The 1980 figure includes diagnostic substances.

Sources: Department of Commerce, Bureau of the Census, *Current Industrial Reports: Pharmaceutical Preparations, Except Biologicals* (data on pharmaceutical preparations); Department of Commerce, Bureau of the Census, *Annual Survey of Manufactures* (other data).

Table 9: **R&D Spending by the U.S. Pharmaceutical Industry, 1980 and 1989**

(in millions of dollars unless otherwise indicated)

	1980	1989
Expenditures		
Total R&D Spending	$1,976.7	$7,330.0
Company-Financed Spending	1,971.6	7,327.9
Spent in the United States	1,544.1	6,019.3
Spent Abroad	427.5	1,308.6
U.S. Government Grants and Contracts for Company-Conducted R&D	5.1	2.1
Total Sales of Ethical Pharmaceuticals	22,513.0	50,139.5
R&D Spending as Share of Sales	8.8%	14.6%
Distribution of R&D Money Spent in the United States by Product Class		
Total Spending	$1,544.1	$6,019.3
Cardiovasculars	18.9%	23.0%
Central Nervous System and Sense Organs	16.2	15.4
Neoplasms, Endocrine System and Metabolic Diseases	14.3	15.2
Anti-Infectives	17.4	15.0
Respiratory	4.8	6.1
Biologicals	3.1	4.7
Gastrointestinal and Genitourinary System	6.4	4.6
Dermatologicals	3.2	2.3
Diagnostics (in vitro)	1.0	2.0
Vitamins	2.3	0.2
Other Products for Human Use	6.9	8.0
Veterinary Preparations	5.1	3.3
Veterinary Biologicals	0.4	0.2
Distribution of R&D Money Spent in the United States by Function		
Total Spending	$1,544.1	$6,019.3
Clinical Evaluation: Phases I, II, III	19.8%	26.7%
Biological Screening and Pharmacological Testing	18.6	16.9
Synthesis and Extraction	15.4	9.8
Pharmaceutical Dosage Formulation and Stability Testing	9.2	9.4
Toxicology and Safety Testing	9.7	7.0
Process Development for Manufacturing and Quality Control	9.0	7.3
Clinical Evaluation: Phase IV	3.7	4.0
Preparation, Submission and Processing of Applications	4.1	3.3
Bioavailability Studies	2.1	2.6
Other	8.4	13.0

Note: Figures pertain only to members of the Pharmaceutical Manufacturers Association. These 100-plus companies produce most of the ethical pharmaceuticals sold in the United States. Both the sales and the R&D figures cover ethical drugs alone.

Source: Pharmaceutical Manufacturers Association, *1989-1991 Annual Survey Report.*